IN THE DRAWINGS

Ex. note

Figures 2A and 2B have been corrected to indicate the presence of *parA* rather than *par* as described in the specification. A red-lined version of the figures is attached showing the change. A replacement page of the revised figures is also enclosed.

## REMARKS

In response to the Office Action mailed July 30, 2002, Applicant respectfully requests the Examiner to reconsider the above-captioned application in view of the foregoing amendments and the following comments. Claims 1-81 are pending. Claims 1, 10-16, 35, and 48-50 are under consideration and Claims 2-9, 17-34, 36-47, and 51-81 have been withdrawn from consideration. Claims 16 and 35 have been amended.

Applicants have amended the specification, figures, and claims of the present application. The specification was amended to correct certain informalities in the disclosure. Figure 2 has been correct to indicate the presence of *parA* rather than *par*. Claim 16 has been amended to delete the phrase "or a fragment thereof." Similarly, Claim 35 has been amended to delete the phrase "or an antigenic fragment thereof." Applicants have made these amendments voluntarily to better define the subject matter of the claimed invention and not because of issues of patentability.

The specific changes to the specification and the amended claims are shown on a separate set of pages attached hereto and entitled VERSION WITH MARKINGS TO SHOW CHANGES MADE, which follows the signature page of this Amendment. On this set of pages, the insertions are underlined while the ~~deletions are stricken through~~.

Claims 1, 10-11, 35, and 48-50 are Novel Under 35 U.S.C. § 102(b)

Claims 1, 10-11, 35, and 48-50 are rejected under 35 U.S.C. §102(b) as being anticipated by McConnell, et al., Infection and Immunity, 56:1974-1980 (McConnell), and Rudin et al., Microbial Pathogenesis, 16:131-139 (Rudin). "Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . . There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention." *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991) (emphasis added). Because anticipation

requires that all the elements of a rejected claim be found in a single reference, Applicants interpret the present rejection as two independent rejections.

Claims 1, 10-11, 35, and 48-50 are novel over McConnell because McConnell does not teach an immunogenic composition comprising a recombinant product of a *csa* operon and a carrier, as recited in Claim 1 or the purified polypeptide sequence expressed from a recombinant *csa* operon, as recited in Claim 35. The Examiner characterized McConnell as teaching "that CS4 expressing E. coli were able to produce antibodies to CS4." McConnell did not isolate the CS4 operon nor *csaE*. On page 1976, second column, McConnell hypothesizes that "[i]t seems likely that CS4 and CS6 were coded for by the same plasmid, since these properties were usually lost together," however, McConnell did not prove this hypothesis. In fact, on page 1977, first column, McConnell states, "Alternatively, the CS4-, CS6-positive strains could carry two distinct plasmids of similar size, only one of which is lost in the CS4-negative derivative." Thus, McConnell does not even suggest with certainty that the genes for CS4 were on the CS6 bearing plasmid.

Claims 1, 10-11, 35, and 48-50 are novel over Rudin because Rudin does not teach an immunogenic composition comprising a recombinant product of a *csa* operon and a carrier, as recited in Claim 1 or the purified polypeptide sequence expressed from a recombinant *csa* operon, as recited in Claim 35. The Examiner stated that Rudin "teaches that CS4 is immunogenic." Rudin describes the use of isolated CS4 fimbria from ETEC to generate an immune response, however, Rudin did not isolate the genes that encode the proteins on CS4 fimbria (*csa* operon and *csaE*). Furthermore, Rudin does not disclose the sequence of the proteins in CS4 fimbria.

In contrast, Applicants have isolated and characterized the genes of the *csa* operon, in particular, *csaE*, and placed them on an expression plasmid, expressed the *csa* operon in a non-ETEC bacteria and generated an immune response in an animal. This distinguishes the subject matter of Claims 1, 10-11, 35, and 48-50 from the McConnell and Rudin references for the reasons set forth above.

In light of the foregoing remarks, Claims 1, 10-11, 35, and 48-50 are not anticipated. Accordingly, the rejection of these claims should be withdrawn.

Claims 1, 12-15, and 35 are Novel Under 35 U.S.C. § 102(b)

Claims 1, 12-15, and 35 were rejected under 35 U.S.C. §102(b) as being anticipated by WO 96/38171 (Cassels). As discussed above, Applicants' claims are directed to the *csa* operon or to *csaE*. Cassels teaches the use of a peptide 26 amino acids in length that is generated by a peptide synthesizer. This peptide, according to the Examiner, is identical to residues 24-60 of *csaB*. In contrast, Applicants' claims are directed to the *csa* operon and/or *csaE*. Cassels did not use *csaE*, either generated using a peptide synthesizer or produced by bacteria. Furthermore, a peptide synthesizer cannot even generate a protein as large as *csaE*. Thus, Cassels does not teach the *csa* operon nor *csaE*.

Because Cassels does not teach all the limitations of the claimed invention, Claims 1, 12-15, and 35 are novel over Cassels. Accordingly, the rejection of these claims should be withdrawn.

Claim 16 is Novel Under 35 U.S.C. § 102(b) and Nonobvious Under 35 U.S.C. § 103(a)

Claim 16 is rejected under 35 U.S.C. §102(b) as being anticipated by McConnell or in the alternative, under 35 U.S.C. §103(a) as obvious over McConnell in view of U.S Patent No. 5,932,715 (Scott), or optionally, in view of Lodish et al., Molecular Cell Biology, Third Edition, pp.252-254, Scientific American Books, Inc., 1995 (Lodish) and further in view of Scott.

Claim 16 is novel under 35 U.S.C. §102(b). Claim 16 recites an immunogenic composition, wherein the recombinant product of the *csa* operon is an expression vector comprising the *csa* operon. McConnell, as stated above, does not teach the *csa* operon nor *csaE*. McConnell does not even teach with certainty that the genes for CS4 were on the CS6 bearing plasmid. Even if McConnell is correct in assuming that the CS4 genes were on the same plasmid as the CS6 bearing plasmid, the CS6 plasmid is approximately 50 megadalton in size (50 Mda corresponds to a plasmid of about 75 kb). Furthermore, this plasmid is a naturally occurring plasmid; it is not an expression vector. Expression vector plasmids are extremely different from naturally occurring plasmids in that the promoters are often inducible or constitutive, they contain a selectable marker, and are not as large as naturally occurring plasmids. Using the naturally occurring plasmid disclosed in McConnell, one cannot isolate the DNA from ETEC, run the DNA on a gel, cut out the band containing the plasmid, then put that plasmid in a non-

ETEC bacteria and have that bacteria express CS4. Thus, McConnell does not teach Applicants' invention.

Because McConnell does not teach every limitation of the claimed invention, this reference does not anticipate Claim 16. Accordingly, this rejection should be withdrawn.

Claim 16 is nonobvious under 35 U.S.C. §103(a). To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success found in the prior art. Third, the prior art must reference must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). The art cited by the Examiner fails to establish a *prima facie* case of obviousness.

The Examiner notes that McConnell teaches the existence of the *csa* operon on a naturally occurring plasmid. The Examiner cites to Lodish to support the argument that the Lodish article's teachings in combination with McConnell, "would allow one of ordinary skill in the art to make an expression vector." Office Action, p.7, ll. 1-2.

The combination of McConnell with Scott or Lodish does not make Applicants' invention obvious. Contrary to the Examiner's assertion, McConnell does not teach how to identify the nucleotides coding for CS4. McConnell was unable to determine with certainty which plasmid contained the CS4 genes. Scott only suggests that other fimbria genes can be expressed in bacteria at the same time as the genes for CS2. Neither Scott nor McConnell provides the genes for CS4.

In contrast, Applicants have isolated and characterized the genes for the *csa* operon, in particular, *csaE*, and placed them on an expression plasmid, expressed the *csa* operon in a non-ETEC bacteria and generated an immune response in an animal. The cited references do not render Claim 16 obvious because they do not teach or suggest an immunogenic composition, wherein the recombinant product of the *csa* operon is an expression vector comprising the *csa* operon, and thus, do not teach all of the limitations of Claim 16.

Additionally, even if McConnell correctly determined the plasmid contaiing the gene for CS4 and one skilled in the art were motivated to attempt to isolate the genes and put the genes on an expression plasmid by using the teachings of Scott or Lodish there would be no reasonable expectation of success because the cited references do not adequately describe how this could be

done. The Examiner has not alleged that there is a suggestion or motivation to combine the cited references to achieve the claimed invention. Also, the Examiner has not demonstrated or even alleged that one of skill in the art would have a reasonable expectation of success in practicing the claimed subject matter based on the narrow disclosures of McConnell and Lodish. Finally, the art cited by the Examiner does not teach or suggest all the claimed limitations as neither reference, alone or in combination, recites an immunological composition wherein the recombinant product of the *csa* operon is an expression vector comprising the *csa* operon. Accordingly, Mcconnell in view of Scott or Lodish cannot support a *prima facie* case of obviousness.

Claims 12-15 are Nonobvious Under 35 U.S.C. §103

Claims 12-15 stand rejected as obvious under 35 U.S.C. §103 over McConnell, in view of Cassels. Neither McConnell nor Cassels teach or suggest an immunogenic composition comprising a recombinant product of a *csa* operon and a carrier. As discussed above, to support a *prima facie* case of obviousness, a reference or references must, *inter alia*, teach or suggest all the limitations of the claimed invention. Because neither of the cited references teach or suggest a recombinant product of a an immunogenic composition comprising a recombinant product of a *csa* operon and a carrier, these references cannot support a *prima facie* case of obviousness. Therefore, the present rejection should be withdrawn.

## CONCLUSION

For the foregoing reasons, it is respectfully submitted that the rejections set forth in the outstanding Office Action are inapplicable to the present claims and specification. Accordingly, early issuance of a Notice of Allowance is solicited.

The undersigned has made a good faith effort to respond to all of the rejections in the case and to place the claims in condition for immediate allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is invited to call the undersigned to discuss such issues.

A one-month extension of time is hereby requested. Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 20 NOV 2002

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## VERSION WITH MARKINGS TO SHOW CHANGES MADE

**In the Specification**

**The paragraph starting at page 5, line 28 has been amended as follows:**

The disclosed invention relates to compositions and methods of using *csa* operon products and the nucleotide and amino acid sequences encoded thereby. One embodiment relates to an immunogenic composition comprising a recombinant product of a *csa* operon and a carrier. Various aspects of this embodiment relate to compositions in which the recombinant product of the *csa* operon is CsaA, CsaB, CsaC, CsaD, CsaE, or a product that is at least 95% homologous to ~~anyone~~ any one of these *csa* operon products. Additionally, the recombinant product of the *csa* operon can comprise the *csa* operon itself.

**The paragraph starting at page 6, line 19 has been amended as follows:**

Additional ~~embodiment~~ embodiments encompass cells containing recombinant the *csa* operon or fragments thereof and vectors comprising the *csa* operon or fragments thereof.

**The paragraph starting at page 26, line 5 has been amended as follows:**

Promoters suitable for use with prokaryotic hosts illustratively include the beta-lactamase and lactose promoter systems (Chang, et al., Nature, 275:~~615~~ 617, 1978; and Goeddel, et al., Nature, 281:544, 1979), alkaline phosphatase, the tryptophan (trp) promoter system (Goeddel, Nucleic Acids Res., 8:4057, 1980) and hybrid promoters such as the *taq* promoter (de Boer, et al., Proc. Natl. Acad. Sci. USA, 80:21-25, 1983). Other functional bacterial promoters are also suitable. Their nucleotide sequences are generally known in the art, thereby enabling a skilled worker to ligate them to a polynucleotide which encodes the peptide of interest (Siebenlist, et al., Cell, 20:269, 1980) using linkers or adapters to supply any required restriction sites.

**The paragraph starting at page 26, line 14 has been amended as follows:**

In addition to prokaryotes, eukaryotic microbes such as yeast cultures can also be used as source for the regulatory sequences. *Saccharomyces cerevisiae* is a commonly used eukaryotic host microorganism. Suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase (Hitzeman, et al., J. Biol. Chem., 255:~~2073~~ 12073, 1980) or other glycolytic enzymes (Hess, et al. J. Adv. Enzyme Reg. 7:149, 1968; and Holland, Biochemistry, 17:4900, 1978) such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-

phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

**In the Claims:**

**Claims 16 and 35 have been amended as follows:**

16. (AMENDED) The immunogenic composition of claim 1, wherein the carrier is a composition comprising the *csa* operon ~~or a fragment thereof~~.

35. (AMENDED) A purified polypeptide sequence expressed from a recombinant *csa* operon ~~or an antigenic fragment thereof~~.